Colorectal Disease

Extended TME in Locally Advanced Rectal Cancer (T4a) and the clinical role of MRI evaluated neo-adjuvant downstaging.

Journal:	*Colorectal Disease*
Manuscript ID:	draft
Manuscript type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Larsen, Stein Gunnar; The Norwegian Radium Hospital, Dep. of Surgical Oncology; Faculty Division Norwegian Radium Hospital Wiig, Johan N; The Norwegian Radium Hospital, Dep. of Surgical Oncology Emblemsvaag, Hanne Line; The Norwegian Radium Hospital, Dep. of Radiology Grøholt, Krystina Kotanska; The Norwegian Radium Hospital, Dep. of Pathology Hole, Knut Håkon; The Norwegian Radium Hospital, Dep. of Radiology Bentsen, Annette; University of Oslo, Faculty Division Norwegian Radium Hospital Dueland, Svein; The Norwegian Radium Hospital, Dep. of Oncology Vetrhus, Turid; The Norwegian Radium Hospital, Dep. of Radiology Giercksky, Karl-Erik; The Norwegian Radium Hospital, Dep. of Surgical Oncology; Rikshospitalet, Surgical Clinic; University of Oslo, Faculty Division Norwegian Radium Hospital
Keywords:	rectal cancer , locally advanced , preoperative chemoradiotherapy , tumour regression grade , magnetic resonance imaging, surgery , histopathology
Abstract:	Objective: To compare the ability of MRI taken before and after neo-adjuvant treatment in locally advanced rectal cancer (LARC) to predict the necessity of extended total mesorectal excision and to evaluate the use of histopathological tumour regression grade (TRG). Methods: Prospective registration of 92 MRI evaluated T4a cancers undergoing elective surgery between 2002 and 2007 in a tertiary referral centre for multimodal treatment of rectal cancer. Results: MRI identifies LARC patients in need of neo-adjuvant treatment. MRI predicted T downstaging in 10% and N downstaging in 59%. After extended total mesorectal excision in 95% of patients, mostly en-bloc resections, 79% R0 resections, 18% R1

	and 3% R2 were obtained. N- and T-stage downstaging occurred in 59% and 10% evaluated by yMRI. There was a linear trend with higher TRG in higher ypT-stage (p<0.01). Preoperative chemo radiotherapy resulted in a higher percent of patients obtaining TRG1-3 compared to patients receiving radiotherapy (79% vs 57%, p=0.02). The pelvic wall was the area of failure in 70% of the R1 resections in M0 patients. Conclusion: MRI after neo-adjuvant treatment did not predict downstaging satisfactorily with tumour cells remaining within areas of fibrosis (TRG2-3) in 55% of the pT4 patients. Therefore, if a R0 resection is the goal, we advocate the optimal surgery in accordance with the pre-treatment MRI. The study has initiated a new approach to histopathological classification of the removed specimen where we introduce a MRI assisted technique for investigating the areas at risk outside the mesorectal fascia in the specimen.

Extended TME in Locally Advanced Rectal Cancer (T4a) and the clinical role of MRI evaluated neo-adjuvant downstaging.

Original article

SG Larsen, MD[1,2], JN Wiig, MD[1], PhD, HL Emblemsvaag, MD[3], KK Grøholt, MD[4], KH Hole, MD[3], A Bentsen[1,2], S Dueland, MD, PhD[5], T Vetrhus, MD[3], K-E Giercksky, MD, PhD[1,2]

[1] Department of Surgical Oncology, the Norwegian Radium Hospital, Rikshospitalet University Hospital.

[2] Faculty Division Norwegian Radium Hospital, University of Oslo.

[3] Department of Radiology, the Norwegian Radium Hospital, Rikshospitalet University Hospital.

[4] Department of Pathology, the Norwegian Radium Hospital, Rikshospitalet University Hospital.[5] Cancer Clinic, the Norwegian Radium Hospital, Rikshospitalet University Hospital.

Corresponding author:

Stein Gunnar Larsen, MD,

Department of Surgical Oncology,

The Norwegian Radium Hospital, Rikshospitalet University Hospital,

Montebello,

N-0310 Oslo, Norway.

Stein Gunnar Larsen, MD,

Faculty Division Norwegian Radium Hospital, University of Oslo,

N-0316 Oslo, Norway.

Tel +47 22 93 40 00, Fax +47 22 93 59 44, E-mail stein.larsen@radiumhospitalet.no

INTRODUCTION

Total mesorectal excision (TME) is widely accepted as the procedure of choice in rectal cancer surgery (1;2). TME has increased long-term survival and reduced local recurrence in general (2;3). In cases with microscopic positive resection margins however, the recurrence rate has been reported to be as high as 80% (4).

Recurrence of locally advanced rectal cancer (LARC) is reduced by preoperative radiotherapy (RT) or chemo radiation therapy (CRT) (5;6), and the 5-year survival of LARC has now increased to more than 50% (7;8).

The surgical strategy in LARC is based on TME but modified to include tumour-suspect tissue outside the mesorectal plane. To plan such an extended TME (ETME) the surgeon needs as accurate preoperative information as possible about the extensiveness of the malignant process. Preoperative magnetic resonance imaging (MRI) is considered the best investigative tool for evaluation of rectal cancer (9-11) and LARC (12), due to superior demonstration of signal differences between fat and soft tissue. MRI's value in identifying tumour infiltration into neighbouring organs and the ability to demonstrate neo-adjuvant downstaging has not been firmly established.

Preoperative CRT will in the majority of cases reduce tumour size. We are aware of only one single report (abstract) evaluating MRI before and after neo-adjuvant therapy in clinical/ radiological T4 cases (n=53) (13). No reports seem to study if the repeat MRI after neo-adjuvant treatment improves the surgical achievement. We have compared the clinical ability of MRI taken before and after CRT to predict the necessary extension of the TME procedure in LARC, the possibility to achieve

a R0 resection and evaluated the use of histopathological tumour regression grade (TRG).

MATERIALS AND METHODS

The Radiumhospitalet Cancer Center is a tertiary referral centre for multimodal treatment of LARC and locally recurrent rectal cancer. In the period from January 2002 until April 2007, 268 patients with primary rectal adenocarcinoma 0-15 cm from the anal verge were included in our prospective database (approved by the Ethical Committee at the University of Oslo). Judged on MRI 99 patients had T3 tumours (invading muscularis propria but not peritoneum or perirectal tissue), 28 had T1-2 tumours and did not receive RT and 26 patients had T4b (involving the peritoneal reflection but not neighbouring organs). The remaining 115 had T4a rectal cancer penetrating the mesorectal fascia and invading other organs or structures. Seven of these did not receive pelvic RT or the treatment was stopped before they had received 50 Gy. Another eight patients were not evaluated with MRI both before and after RT, four had MRI of suboptimal quality, and three patients were surgically explored and found inoperable due to abdominal carcinomatosis or to extensive liver metastases. One patient was excluded due to previous history of pelvic malignancy. Known metastatic disease (n=18) was not an exclusion criterion by itself. Thus 92 patients with T4a rectal cancer with neo-adjuvant treatment were included in the study. The staging workup included endoscopy, biopsy, digital exploration and bimanual palpation in general anaesthesia before and after RT.

Stage evaluation

The TNM system classifies carcinomas according to depth of invasion of the primary tumour, presence of regional lymph node metastases and distant metastases. T- and N-stages were evaluated by MRI both before (cmrT, cmrN) and after neo-adjuvant therapy (ymrT, ymrN) as well as after histopathological examination (ypT, ypN) (14). We have

preferred to record the R stage as local R stage judged by the removed specimen (R0 = microscopically free circumferential and distal margins, R1 = microscopically involved margins ≤ 1 mm from resected margin and R2 = macroscopic residual cancer in the pelvis or no resection).

Magnetic resonance imaging

The treatment of rectal cancers varies according to tumour stage. Three specialists in gastrointestinal radiology performed all investigations with the same MRI technique and validated protocols as they used in the MERCURY study (10;11). Evaluation of lymph nodes followed the criteria developed by Brown (15). All patients were discussed at the multidisciplinary staff meeting and one of the radiologists (HLE) crosschecked all data. The patients had two investigations, the first before neo-adjuvant therapy (cMRI) and the second at a median of 33 days (range 18 – 91 days) after completed treatment (yMRI). We considered a MRI distance of >1 mm from tumour tissue to surrounding structures necessary to avoid resection of any structure or organ. A distance ≤ 1 mm to an organ or a structure was characterized as threatening the organ or structure. However, a structure was evaluated on MRI as infiltrating an organ or structure only if the tumour grew into it. After CRT change of tumour T2-signal to low as in fibrosis was mostly evaluated as potential residual tumour, according to the radiologist's awareness of the difficult detection of small islets of tumour within fibrosis.

MRI was performed using a 1.5-T MR scanner and phased-array coil. Two-dimensional fast spin-echo sequences were preformed. High-resolution T2W images were obtained in a plane perpendicular to the mesorectum at the site of tumour and suspicious lymph

nodes. In addition, high-resolution T2W images were obtained in coronal planes in low rectal cancers. The magnetic imaging details are given in table 1.

Preoperative chemotherapy

CRT was not routinely given until December 2003 but seven patients received chemotherapy (5-FU/ leucovorin) as part of a randomized multicenter trial (Nordic LARCS-A Trial). After December 2003, 93% of the patients received 5-FU/ leucovorin (n=44) or oxaliplatin/ 5-FU/ leucovorin (n=9). The patients who received CRT in the last period were compared to those given RT in the first period.

Preoperative radiotherapy

The RT was based on a CT dose planning system and the patients received a median of 50 Gy (50-64) preoperative RT; 46 Gy in 2 Gy fractions towards the pelvis and a boost of 4 Gy in two fractions towards the tumour. Seven patients received additional fractions of 1-12 Gy due to treatment discontinuity.

Surgery

Total mesorectal excision technique (TME) was performed with extended dissection outside the mesorectal fascia to obtain “en bloc” resection of tumour and this was achieved in 95%. The procedure was often a joint venture by gastrointestinal surgeons, urologists and plastic surgeons. The surgical procedures were performed a median of 56 days (36-119) after the end of RT and a median of 20 days (4-84) after MRI evaluation. Peroperatively it was often difficult to identify the surgical planes between tumour and surrounding organs. As it could not be definitely decided if the adherences were due to tumour tissue or fibrosis, even in patients with non-infiltration on yMRI, the

surgeon had to decide during the procedure whether to resect the whole or only a part of the affected organ. In some cases, previously undetected distant metastases were found during surgery and a less radical procedure performed in the pelvis. Resections of fascia or muscle fibres of the piriformis or obturator muscle were considered as resection of the pelvic wall. Resection of levator ani was performed as part of an abdominoperineal resection (APR) and in some patients the coccyx or part of the sacrum was resected as well.

Pathology

Examination of removed specimens were performed according to the MERCURY protocol (10;11). The specimens were opened from the ends until 2 cm above/ below the tumour and fixed in formalin. The unopened area was cut in 5 mm slice thickness transversely and large-mount preparations were made of tumour slices that showed the maximum depth of penetration and with the tumour close to the circumferential resection margin (CRM). A histological complete response (ypT0) was achieved if the pathologist was unable to demonstrate any intact viable tumour cells within the operative specimen. The presence of mucin lakes without adjacent cells was defined as a complete response. TRG were analyzed and classified according to Bouzourene (16) based on the presence of residual tumour cells and the extent of fibrosis. In Grade 1, there are no residual tumour cells and fibrosis extends through all the layers of the rectal wall. Grade 2 has rare residual tumour cells scattered throughout the fibrosis. Grade 3 involves more residual tumour cells but the fibrosis still dominates. Grade 4 demonstrates residual tumour cells outgrowing the fibrosis whereas in Grade 5 there is lack of tumour regression. The same pathologist (KKG) with experience from the MERCURY study evaluated all but one specimen.

Statistical analysis

Association between categorical variables were assessed using chi-square tests (Pearson and linear-by-linear). Differences between groups of quantitative variables were tested using Mann-Whitney test. The downstaging of T- and N-stages in Table 3 were evaluated by the McNemar-Bowker Test of symmetry or McNemar Test. P values of 0.05 or less were regarded as significant. Calculations were performed using the Statistical Package for the Social Sciences® program, version 15.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Ninety-two patients with T4a primary rectal cancer based on cMRI evaluation before neo-adjuvant treatment were included in this study and demographic data regarding resection status are given in Table 2. Evaluated by MRI, pelvic organs (uterus, vagina, bladder, vesicle and prostate) were affected in 32 patients, perirectal structures (pelvic muscles, nerves, vessels, sacrum and ureter) in 12 patients and both pelvic organs and perirectal structures in 48 patients. After neo-adjuvant treatment, a R0 resection was obtained in 73 patients (79%), a R1 resection in 16 patients (18%) and R2 resections in three patients (3%). All R2 resections and six of the R1 resections had distant metastases (inoperable liver, lung or lymphatic metastasis) at the time of surgery. In the remaining ten R1 resections the anatomical site of failure was on the pelvic wall in seven patients, the peritoneal reflection in two and the prostate in one patient. The latter was the only patient with an unintended R1 resection for infiltration of a pelvic organ and had peripheral resection of the prostate. If patients with known ir-resectable metastases were excluded from the study, a R0 resection rate was obtained in 63 of 74 patients (85%) and R1 resections in the rest of the patients.

There was no difference in age between the R0 and the R1/R2 resection groups. However, in females more R0 resections and no R2 resections were obtained ($p<0.01$). In 85% of patients who received CRT a R0 resection was obtained compared to 64% in patients who received only RT ($p<0.05$). The time from end of radiation therapy to surgery and the type of surgery performed were similar in the two groups. However, the mean length of the tumours after preoperative treatment was significantly larger in patients receiving a non-radical resection ($p<0.01$). More pelvic organ resections were performed in R0 patients (78% versus 42%, $p<0.01$ and more downstaging of N-status

occurred in the R0 resection group compared to R1/R2 resection group (58% versus 21%, p<0.01).

The effect of neo-adjuvant treatment on MRI based T and N staging is shown in Table 3. After completion of neo-adjuvant treatment, downstaging from pT4a occurred in only 9 of 92 patients (10%), and only to pT3. The pre-treatment N stage by cMRI was; 11 N0, 17 N1 and 64 N2. MRI examinations after neo-adjuvant treatment showed an N-stage downstaging in 48 of 81 patients (59%) and 35 of 81 patients (43%) obtained a N0 disease. Only one patient was upstaged (1%).

Five of the nine patients suggested by yMRI to be downstaged to T3 were further confirmed to be ypT3 tumours (Table 3). Of the other four, three were ypT0-2 tumours and one had an ypT4 tumour. Of the 83 patients determined by yMRI to be T4 tumours, only 32 were confirmed by pathological examination to be ypT4 tumours. Fifty-one patients had a downstaging at pathological examinations that was not detected by yMRI (55%). Overall, similar staging by yMRI and histopathological evaluation was obtained in 40% of the patients. By pathological evaluation, only five of the downstaged had received R1 resections, four because of microscopically involved CRM next to the tumour and one next to an infiltrated lymph node.

Totally, in 37 patients the staging in MRI after neo-adjuvant treatment and the classification in histopathology were similar. However, in 51 patients (55%) the histopathology staged the patients as T0-T3 (38 ypT3, 5 ypT1-2 and 8 ypT0) even though MRI had staged the patient as T4.

Histopathological evaluation revealed nine patients (10%) with a complete pathological response to neo-adjuvant treatment (ypT0) (Table 3). In a further 54% the primary tumour was located within the mesorectal fascia. Thus if we had performed an ordinary TME operation instead of an extended one, there would have been R1/ R2 resections in all 33 patients with ypT4 (36%) in addition to 7 R1 in the tumours within the mesorectal fascia (7%), totally 43%. This would have been more than the double of the 21% obtained after performance of ETME.

Comparing N-staging by MRI after neo-adjuvant treatment with pathological examination as a reference standard showed that 47 of 92 (51%) were similarly staged by MRI, whereas 13 % were under-staged and 36% were over-staged by yMRI (Table3b). 37 of 45 patients (82%) with a MRI N0 stage after neo-adjuvant treatment had a confirmed histopathological ypN0 disease.

The relation between TRG and ypT-stage is shown in Table 4. Among the 33 ypT4 tumours 18 were TRG2-3 and 15 were TRG4-5 demonstrating that we found tumour cells outside the mesorectal fascia scattered within fibrosis in as much as 55% of the ypT4 group. All the tumours resulting in an ypT1-2 had TRG2-3, whereas all ypT3-4 tumours had TRG2-5 ($p<0.01$). Preoperative CRT resulted in a higher percent of patients obtaining a TRG1-3 compared to patients receiving RT (79% vs 57%, $p=0.02$) (Table 5).

In spite of the modest T downstaging on MRI, a reduction in length of tumour of more than 30% was achieved by neoadjuvant treatment in 45% of the tumours (17).

The relation between yMRI infiltration and up-/downstaging from cMRI, performed surgery and infiltration of organs and structures are given in table 6. Threatened tumour infiltration after neo-adjuvant treatment was described by the yMRI examination in 89 pelvic organs, in 22 cases on the pelvic wall and in 36 cases on the pelvic floor. Surgery was performed on 70 of the pelvic organs with threatened infiltration on MRI (≤ 1mm distance to organ), including all ten bladders but no more than 14 of 21 affected vaginas and 14 of 19 prostates. The infiltration was confirmed by pathological examination in 23 pelvic organs and, in addition, fibrosis or mucus in the organs was found in 15 pelvic organs. Totally, signs of infiltration into pelvic organs were confirmed by histopathological examination in a large proportion where yMRI had documented threatened margins: bladder (90%), vagina (71%), seminal vesicles (50%) and prostate (43%).

DISCUSSION

The definition of LARC varies and some include any T-stage with N+ disease. We have included only patients with T4a cancers that on cMRI infiltrated into surrounding pelvic organs. Thus, the tumours in our patients have a more extensive growth than in most other studies on this topic. Although MRI is considered the best method for examination of LARC, in a material without neo-adjuvant treatment, the accuracy of organ infiltration measured by yMRI was 80% judged by the pathology examination of the removed specimen (18). To reduce inter-individual differences, colleagues with experience from the previous MERCURY study performed the MRI and pathology examinations.

During our study period the clinical value of the yMRI had not been clarified and in some cases the tumour shrinkage following neo-adjuvant treatment lead the surgeon to perform a less extensive resection than cMRI indicated.

A few prospective studies as well as retrospective audits have focused on MRI and histopathologic assessment of the specimen in rectal cancer surgery, irrespective of tumour stage (3;9-11;19-21). MRI in LARC before neo-adjuvant treatment compared to the removed specimen has been the focus of few reports (19;22;23) or when being addressed contained a very small proportion of mrT4 tumours (21;24-28). In one study LARC and recurrent rectal cancer were evaluated together (18) but no study to our knowledge has tried to evaluate the clinical importance of the preoperative MRI after neo-adjuvant treatment or TRG data from a relatively large number of MRI diagnosed T4 tumours.

Resection margins and resection status

MRI's ability to demonstrate signal differences between different soft tissues are important to discriminate between structures on the pelvic sidewall as well as to detect tumour invasion. Accordingly, MRI is considered the superior tool in predicting the CRM status by TME, depth of extramural tumour and nodal status (9-11). In T4a rectal tumours, however, the mesorectal fascia is involved by tumour, and surgery must be extended beyond the TME plane. MRI predicted clear resection margins in 98% R0 resections of patients given RT or CRT in the MERCURY study, but predicted no more than 44% of the patients when only R1/R2 resections were achieved (11).

There was only one R1 resection after performance of total prostatectomy in 17 patients. However, all five cases with a partial resection of the prostate resulted in a R1 resection. The failure against the pelvic wall in four of five and distant metastases in three reduced the willingness to extensive and mutilating local procedures.

Histopathological proven infiltration in a pelvic organ or the pelvic wall was found in 21 patients and 14 of them were classified as R0 resection. Without an extended TME these patients would have been left with tumour tissue. In addition, a substantial number of patients, which is difficult to estimate precisely, would have been left with a minimal distance to tumour tissue (≤1 mm) resulting in a R1 resection. However, in patients with a short life expectancy as in disseminated disease, co-morbidity or very high age, performance of an ordinary TME instead of the extended TME could be the best solution. This might even be the case in large tumours threatening the lateral margins in multiple areas where potential extended procedures might lead to high risk of a non-radical resection and reduced quality of life.

Local recurrence rate is inversely related to the CRM and ≤ 1mm or ≤ 2mm lateral margins in the specimen have been advocated (2;4;29). MRI evaluated, margins ≤ 1mm (11) or ≤ 2mm (12) been considered as threatened lateral margins of non-T4 cases. Neither the necessary margins nor the need for removal of entire compartments are known when the tumour infiltrates adjacent organs or structures.

T downstaging

We found 10% T downstaging evaluated by cMRI and yMRI, not unlike 17% observed by Allen (26) in a small study on 30 patients including only nine cmrT4 patients. In contrast, Baatrup et al found downstaging in seven of fourteen cmrT4 cases after 60 Gy preoperative CRT with 5-FU (30). In our study, the total accuracy detected by yMRI was only 40% and overstaging in 59% of the cases with pathology as a reference standard. These results are not unlike the report from Kuo on 14 T4 tumours given neo-adjuvant treatment (19) with 47% total accuracy of yMRI compared to histological examination. They report all ypT4 correctly staged, however ypT0, ypT1, ypT2, ypT3 were overstaged in 80%, 100%, 57% and 30%, respectively.

Due to the problem of detecting islets of viable tumour within fibrosis or mucin deposits, our radiologists have interpreted the fibrosis/ mucin as possibly containing tumour leading to a low proportion of downstaging in T-stage. However, our results with a total downstaging in T4a level from cMRI to final pathology of 64% is similar to reported in small series of 22 and 18 T4 tumours (73%-76%) (3;22).

The discrepancy between yMRI and the evaluation of the specimen could also be explained by further downstaging of tumour due to the time lag between MRI and

surgery. However, the median time to surgery was not more than 20 days and only five patients waited more than six weeks. Vliegen recently showed a substantial overstaging of tumour invasion in the mesorectal fascia in yMRI, which occurred in 36% and 22% of cases by two dedicated observers (12), demonstrating the inter-individual differences in evaluation.

N downstaging

By preparation of the specimen we routinely leave the mesorectum intact during fixation. A higher yield of lymph nodes might have been obtained if the mesorectum was squeezed for lymph nodes in the unfixed state. On the other hand, our application of the recently suggested important characteristics for lymph nodes, like irregular borders and signal intensity characteristics by MRI, in addition to general morphological criteria such as size and shape of the node might influence the number of metastatic nodes detected by MRI (15;31).

mrN downstaging after the neo-adjuvant treatment as evaluated by yMRI was seen in 70% of the patients. yMRI N downstaging was also observed even when the primary tumour was not decreased in size or stage. Our result is similar to 64% and 68% previously reported (19;26). The accuracy between MRI after neo-adjuvant treatment and the final histopathology was 51% whereas MRI overstaging was 36% and understaging 13%. Understaging could be explained if pathological lymph nodes were not removed surgically or not detected by the pathologist. In 43% of the patients a N0 disease, evaluated by MRI, after CRT was obtained which is similar to 46% reported after CRT in a LARC study with only 8% mrT4 cases (24).

TRG, fibrosis and yMRI-assisted histopathology

Our radiologists have interpreted the fibrotic scar as possibly containing tumour, presuming that small islets of tumour cells would not make any visible difference of the MRI-signal. Within a voxel (the smallest imaging element), the dominating tissue will determine the signal. According to the dominance of fibrosis in TRG2-3, the yMRI signal from scattered tumour cells within fibrosis will be that of fibrosis. The signal from tumour cells will not be enough to alter the signal of the whole voxel, in contrast to the situation before treatment where tumour cells usually are densely organized and not scattered. Hence cMRI will more accurately demonstrate the presence of tumour. If tumour cells and fibrosis were more separated as in TRG4-5, the signals might be discriminated and therefore TRG4-5 is more obviously recognized due to less fibrosis.

We would expect that all 83 ymrT4 cases could result in a local recurrence if only a TME had been performed. However, 51 of these had a histopathological stage less than ypT4, and therefore no verified tumour outside the mesorectal fascia even though the yMRI suggested so. Eight of them were TRG1, 24 TRG2, seven TRG3 and 12 TRG4 suggesting that the majority of the tumours contained mostly fibrosis. Accordingly, the 39 patients with TRG1-3 can be very difficult to classify histopathologically due to the amount of tumour with a large critical margin laterally. CRT induced fibrosis, necrosis and mucus in the tissue which produced difficulties in evaluating resected organs, structures and the status of the resection margins.

We presume that a MRI assisted technique for the pathological investigation of the areas at risk in an optimal histopathological slide can be of great value in discovering small nests of tumour tissue outside the mesorectal fascia (Figure 1). This could be

important for future staging and planning of treatment. We will later address the results with this new technique from an ongoing study.

Brown et al found the discrimination of tumour from radiation-induced fibrosis so difficult by yMRI after long course RT that they were not able to measure the depth of extramural spread and therefore excluded all six patients with this treatment (32). They also suggested it likely to be more useful to compare pre-treatment MRI (cMRI) with histopathology of the resected specimen to determine the extent of tumour regression.

Our TRG1-3 frequency of 70% is higher than 59% reported by Bouzourene in their study with only RT as neo-adjuvant treatment for LARC (16). The difference can be due to our inclusion of 53 patients given preoperatively CRT (58%) which was found to improve the TRG grades.

In a published abstract, scattered tumour cells within the fibrosis, at or outside the mesorectal fascia were reported in 50% of pT4 tumours treated with RT or CRT (13) which is similar to our 55% of TRG2-3 in this group. These observations strengthen the need for surgical resection of all fibrosis in locations where MRI before treatment showed tumour to obtain optimal results. There has been a tendency over the last years to perform an increasing rate of low anterior resections (LAR's) in advanced rectal cancer (33). The results show that fibrosis left in situ in advanced cases may contain viable tumour cells, which may increase the late recurrences. In this way, the reported 28% local relapses after RT occurring more than 5 years after surgery could be explained (34). Thus a longer observation interval may be necessary to determine the true local recurrence rate after CRT.

The histopathological complete response rate (ypT0) after neo-adjuvant CRT vary with the type of chemotherapy added to the RT, the selection of patients, the proportion of T-stages and also with the irradiation regimen (8;35;36). We found 10% histological proven complete response in our study of only T4a tumours. The proportion may be increased by addition of induction chemotherapy with new drugs (22;37) and the downstaging and downsizing of tumour may lead to less extensive resections in the future.

Reduction in tumour size

Our study shows reduction in length of tumour after neo-adjuvant treatment measured by MRI, and further reduction of maximal tumour diameter evaluated in the specimen. Because the maximal tumour diameter is a measure of axial growth of the tumour, it is not surprising that we found it to be a marker for R1/ R2 resections and for advanced T stages. Torkzad et al (25) showed a clear correlation between tumour volume and percent volume reduction after RT by MRI and histopathology. Kim et al (38) reported a significant difference in tumour volume and percent volume reduction rates between patients whose tumours were downstaged and those that were not in a study with 4% T4 tumours. Tumor size is a factor known to influence histopathological downstaging of rectal cancer after CRT. Decrease in tumour size, according to the RECIST criteria of more than 30% occurred in 41 of our patients (45%) (17). Allen et al (26) found a decrease of more than 30% in tumour size in 63% of cases, but their report contains only nine T4 tumours, and in addition 19 T3 and two T2 tumours. A recently published, small study with 28% T4 tumours did not find that a reduction in tumour volume was a marker for N downstaging or TRG (39).

Infiltration of organs/ structures

The area of failure after intentional curative resection was the pelvic wall in seven of our ten R1 resections (70%) with M0 disease. In six of seven cases we had signs of threatened organ infiltration on MRI both before and after neo-adjuvant treatment and in five of seven after neo-adjuvant treatment. Five of the seven patients had yMRI classified pathological lymph nodes on the pelvic wall. Among the ten failures, there were only two women. The explanation to this might be the wide female pelvis, where the vagina/ uterus often is a barrier for further spread in the anterior direction, and therefore is easier to eradicate than the narrow male pelvis (7).

MRI is still the most accurate modality in demonstrating involvement of neighbouring organs. The MRI evaluated threatened organ and structure infiltrations, before and after neo-adjuvant treatment, corresponds to surgery on performed pelvic organs. yMRI showed threatened infiltration (growing into organ or structure or ≤ 1 mm of organ or structure) in 89 pelvic organs. Peroperatively we resected 70 and evaluated the remaining 19 as not infiltrated. Only in 34%, we were able to confirm the tumour cells in the organ, but in another 15 patients (21%), we found fibrosis as sign of infiltration before neo-adjuvant treatment.

Should findings in MRI after CRT/ RT alter the operative strategy?

The tissue reaction to neo-adjuvant treatment makes yMRI difficult to evaluate. Videhult et al reported that among patients with no agreement between ymrCRM and ypCRM, half of them received long course RT (20). Fibrosis possibly containing scattered tumour cells might be handled in two ways; resected or left in situ. The first option would lead to

a more, and sometime needlessly extended operation, probably also with permanent diverting stoma whereas the latter might leave tumour cells in the pelvis, probably resulting in more cases of local relapse after some years.

In some cases the repeat MRI after CRT clearly shows retraction of pathological tissue from structures thought to be infiltrated or adjacent to tumour on MRI before CRT, thus showing overstaging/ misinterpretation of the tumour in the first place. In these cases, the repeat MRI of course might alter the operative strategy.

CONCLUSION

Radiological assessment with MRI of the pelvis identifies patients in need of neo-adjuvant treatment in LARC. Eighty-five percent R0 resections were obtained in M0 patients after MRI diagnosed infiltration into adjacent organs (cmrT4a). ETME was performed in 95% of the patients, mostly as en-bloc resections. However, the non-radical resections were not predicted in advance and the remaining tumour tissue were nearly always located on the pelvic wall.

MRI after neo-adjuvant treatment did not predict downstaging satisfactorily and in patients with histopathology proven T4, fibrosis with scattered tumour cells remained in the 18 patients (55%) with TRG2-3. Therefore, surgery should be performed in accordance with the pre-treatment MRI to obtain optimal result. Otherwise, late recurrence may develop from scattered tumour cells within the fibrosis that might be left in situ. MRI after end of neo-adjuvant treatment gives little new information for planning of surgery, and is mostly important in discovering disease progression.

In the future, more effective CRT protocols may reduce the need for ETME operation due to increased downstaging of tumour. The study has initiated a new approach to histopathological classification of the removed specimen where we introduce a MRI assisted technique for investigating the areas of risk outside the mesorectal fascia in the specimen.

Table 1. Details of the MRI used in the study.

Parameter	Sagittal FSE	Axial FSE T2W: From pelvic floor to promontorium	Axial FSE T1w: ParallelsT2W	High resolution FSE T2W
Field of view	20 cm	20 cm	20 cm	16 cm
Slice thickness	4 mm	5 mm	5 mm	3 mm
Intersection gap	1 mm	1 mm	1 mm	0 mm
Matrix	≥ 256 x 256	≥ 256 x 256	≥ 256 x 256	≥ 256 x 256
TE (Echo time)	85 ms	85 ms	minimum	85 ms
TR (Repetition time)	≥ 3000 ms	≥ 3000 ms	400-700 ms	≥ 3000 ms

Table 2. Patient - and treatment characteristics regarding R status.

Parameter		R0 resection (n=73)		R1-2 resection (n=19)		
		n or median	range	n or median	range	P value
cMRI organ involvement	pelvic perirectal both	26 10 37		6 2 11		p=0.83[1]
Gender	male female	41 32		17 2		p<0.01[1]
Chemotherapy	yes no	45 18		8 10		p<0.05[1]
Age	year	60.5	23-82	67	29-81	p=0.33[3]
Operation after radiotherapy	days	56	36-119	55	39-113	p=0.25[3]
Maxiamal tumour diameter	(mm)	40	0-110	60	35-170	p<0.01[3]
Pelvic organ resection performed	Yes No	57 16		8 11		p<0.01[1]
Histopathological infiltration	Pelvic Perirectal Not infiltrating	13 1 59		5 2 12		P=0.09[1]
Downstaging of N-status	Yes No	42 31		4 15		p<0.01[1]
tumour level on MRI	cm	5	0-15	4	1-10	p=0.72[3]
cmrN stage	N0 N1 N2	11 11 51		0 6 13		p=0.48[2]
M stage	M0 M1	63 10		11 8		p=0.01[2]
ymrT stage	ymrT3 ymrT4	7 66		2 17		p=1.0[1]
cMRI length of tumour	mm	79	32-140	92	50-150	p=0.08[3]
yMRI length of tumour	mm	48.5	0-130	67	10-130	p=0.01[3]
MRI reduction of tumour length	(mm)	20.5	(-60) – 93	19	(-5) – 73	p=0.29[3]
TRG	1 2 3 4 5	9 31 13 15 5		0 6 5 6 2		p=0.07[2]
ypT	ypT0 ypT1-2 ypT3 ypT4	9 7 36 21		0 0 7 12		p<0.01[2]
ymrN	N0 N1 N2	41 11 21		4 8 7		p=0.06[2]
ypN	N0 N1 N2	60 9 4		6 5 8		p<0.01[2]
Pelvic wall resection	yes no	49 24		15 4		p=0.41[1]
APR LAR Hartmann		40 26 7		11 5 3		p=0.62[1]
Histopathological differentiation	High moderate low	44 16 5		9 3 4		p=0.16[2]

[1]Pearson Chi-Square; [2]Linear-by-linear; [3]Mann-WhitneyTest

Table 3a. MRI-evaluated T- and N stages before - and after CRT/ RT.

MRI-evaluated T-stages pre-CRT vs. post-CRT					
	ymrT0	ymrT1-2	ymrT3	ymrT4	Total
mrT4	0	0	9	83	92

MRI-evaluated N-stage pre-CRT vs. post-CRT				
	ymrN0	ymrN1	ymrN2	Total
mrN0	10	0	1	11
mrN1	11	6	0	17
mrN2	24	13	27	64
Total	45	19	28	92

p<0.01, McNemar-Bowker Test.

Table 3b. MRI-evaluated T- and N stages after CRT/ RT versus pathology.

T-stages post-CRT vs. histology					
	ypT0	pT1-2	ypT3	ypT4	Total
ymrT3	1	2	5	1	9
ymrT4	8	5	38	32	83
Total	9	7	43	33	92

p<0.01, McNemar Test.

N-stages post-CRT vs. histology				
	ymrN0	ymrN1	ymrN2	Total
ypN0	37	11	18	66
ypN1	6	4	4	14
ypN2	2	4	6	12
Total	45	19	28	92

p<0.01, McNemar-Bowker Test.

Table 4. Tumour regression grade and histopathologic stage (16).

Histopathologic stage	TRG1	TRG2-3	TRG4-5	Total
ypT0	9	0	0	9
YpT1-2	0	7	0	7
ypT3	0	30	13	43
ypT4	0	18	15	33
Total	9	55	28	92

$p<0.01$, linear-by-linear.

Table 5. Tumour regression grade and preoperative treatment (16)

	TRG1	TRG2-3	TRG4-5	Total
CRT	5	37	11	53
RT	1	15	12	28
Total	6	52	23	81

p= 0.04, linear-by-linear.

Table 6. Relation between threatened organs and structures on MRI, performed surgery and histopathology.

Organ	Threat-ened structures on second MRI	Upstaged from first MRI	Down-staged from first MRI	Surgery on affected organ	Histopathology		
					Infil-tration	Fibro-sis/mu cus	Not infiltration or fibrosis
Bladder	10	2	4	10	6	3	1
Vesicula seminalis	25	1	0	20	7	3	10
Prostate	19	2	3	14	3	3	8
Vagina	21	1	3	14	5	5	4
Uterus	10	0	0	9	1	1	7
Small bowel	4	0	2	2	1		1
m. puborectalis/ m. levator ani	36	0	2	35	4	-	-
Pelvic wall/ sacrum/ureter/ wessels/ m. piriformis	22	3	3	19	1	-	-

Threatened organ- or structure infiltration on MRI: Tumour evaluated as growing into organ or structure or ≤ 1 mm of organ or structure.
Histopathological infiltration: Vital tumour cells found in adjacent organ or structure.

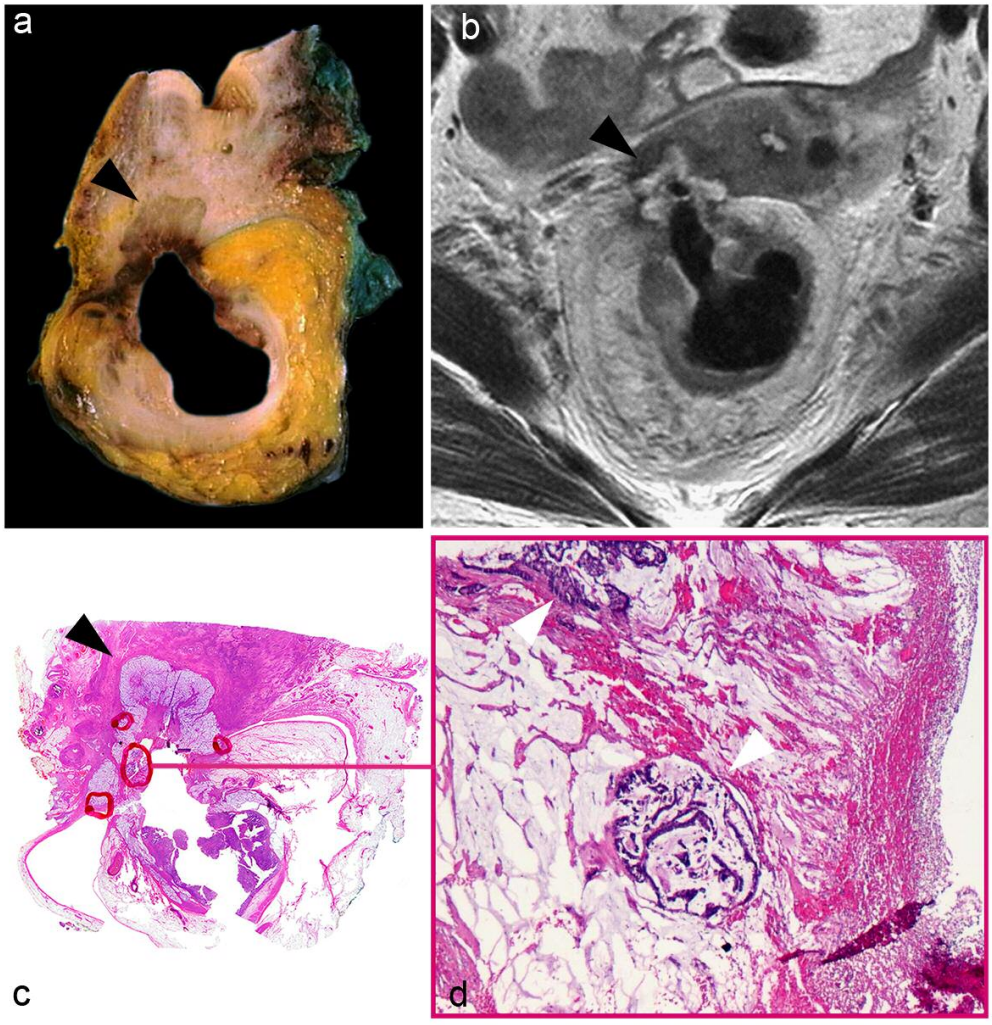

Figure 1. Tumour islets within mucinous infiltration (black arrowheads) of the uterine cervical stroma. (a) Resection specimen slice. (b) Corresponding transversal T2-weighted MRI obtained after radiation theraphy. (c) Corresponding whole-mount histology (haematoxyline and eosine stained). Four islets of tumour where present (red circles). (d) Original magnification x 25 of the largest tumour deposits (white arrowhead).
99x102mm (300 x 300 DPI)

Reference List

(1) Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Archives of Surgery 1998;133(8):894-9.

(2) Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. British Journal of Surgery 2002;89(3):327-34.

(3) Kuo LJ, Liu MC, Jian JJ, Horng CF, Cheng TI, Chen CM, et al. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? Ann Surg Oncol 2007 Oct;14(10):2766-72.

(4) Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986 Nov 1;2(8514):996-9.

(5) Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. New England Journal of Medicine 2004;351(17):1731-40.

(6) Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006 Sep 14;355(11):1114-23.

(7) Larsen SG, Wiig JN, Dueland S, Giercksky KE. Prognostic factors after preoperative irradiation and surgery for locally advanced rectal cancer. European Journal of Surgical Oncology (EJSO) 2008 Apr;34(4):410-7.

(8) Vauthey JN, Marsh RW, Zlotecki RA, Abdalla EK, Solorzano CC, Bray EJ, et al. Recent advances in the treatment and outcome of locally advanced rectal cancer. Ann Surg 1999 May;229(5):745-52.

(9) Beets-Tan RGH, Lettinga T, Beets GL. Pre-operative imaging of rectal cancer and its impact on surgical performance and treatment outcome. European Journal of Surgical Oncology 2005 Aug;31(6):681-8.

(10) MERCURY Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. Radiology 2007;243(1):132-9.

(11) MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006 Oct 14;333(7572):779.

(12) Vliegen RF, Beets GL, Lammering G, Dresen RC, Rutten HJ, Kessels AG, et al. Mesorectal fascia invasion after neoadjuvant chemotherapy and radiation therapy for locally advanced rectal cancer: accuracy of MR imaging for prediction. Radiology 2008 Feb;246(2):454-62.

(13) Tanaka S, Palmer G, Martling A, Lindholm J, Holm T. Tumor cells in peri-tumoural fibrosis after neoadjuvant treatment in locaslly advanced rectal cancer (abstract). Colorectal Disease 8 (s4) , 1-2 doi:10.1111/j.1463-1318.2006.01081.x . 2008.
Ref Type: Abstract

(14) Moran B, Brown G, Cunningham D, Daniels I, Heald R, Quirke P, et al. Clarifying the TNM staging of rectal cancer in the context of modern imaging and neo-adjuvant treatment: 'y''u' and 'p' need 'mr' and 'ct'. Colorectal Dis 2008 Mar;10(3):242-3.

(15) Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 2003;227(2):371-7.

(16) Bouzourene H, Bosman FT, Seelentag W, Matter M, Coucke P. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002 Feb 15;94(4):1121-30.

(17) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000 Feb 2;92(3):205-16.

(18) Beets-Tan RG, Beets GL, Borstlap AC, Oei TK, Teune TM, von Meyenfeldt MF, et al. Preoperative assessment of local tumor extent in advanced rectal cancer: CT or high-resolution MRI? Abdominal Imaging 2000;25(5):533-41.

(19) Kuo LJ, Chern MC, Tsou MH, Liu MC, Jian JJ, Chen CM, et al. Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy. Diseases of the Colon and Rectum 2005;48(1):23-8.

(20) Videhult P, Smedh K, Lundin P, Kraaz W. Magnetic resonance imaging for preoperative staging of rectal cancer in clinical practice: high accuracy in predicting circumferential margin with clinical benefit. Colorectal Dis 2007 Jun;9(5):412-9.

(21) Maretto I, Pomerri F, Pucciarelli S, Mescoli C, Belluco E, Burzi S, et al. The potential of restaging in the prediction of pathologic response after preoperative chemoradiotherapy for rectal cancer. Ann Surg Oncol 2007;14(2):455-61.

(22) Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, et al. Neoadjuvant Capecitabine and Oxaliplatin Followed by Synchronous Chemoradiation and Total Mesorectal Excision in Magnetic Resonance Imaging-Defined Poor-Risk Rectal Cancer. J Clin Oncol 2006 Feb 1;24(4):668-74.

(23) Rao SX, Zeng MS, Xu JM, Qin XY, Chen CZ, Li RC, et al. Assessment of T staging and mesorectal fascia status using high-resolution MRI in rectal cancer with rectal distention. World Journal of Gastroenterology 2007;13(30):4141-6.

(24) Chen CC, Lee RC, Lin JK, Wang LW, Yang SH. How accurate is magnetic resonance imaging in restaging rectal cancer in patients receiving preoperative combined chemoradiotherapy? Diseases of the Colon and Rectum 2005;48(4):722-8.

(25) Torkzad MR, Lindholm J, Martling A, Cedermark B, Glimelius B, Blomqvist L. MRI after preoperative radiotherapy for rectal cancer; correlation with histopathology and the role of volumetry. European Radiology 2007;17(6):1566-73.

(26) Allen SD, Padhani AR, Dzik-Jurasz AS, Glynne-Jones R. Rectal carcinoma: MRI with histologic correlation before and after chemoradiation therapy. AJR 2007;188(2):442-51.

(27) Blomqvist L, Holm T, Nyren S, Svanstrom R, Ulvskog Y, Iselius L. MR imaging and computed tomography in patients with rectal tumours clinically judged as locally advanced. Clin Radiol 2002 Mar;57(3):211-8.

(28) Kulkarni T, Gollins S, Maw A, Hobson P, Byrne R, Widdowson D. Magnetic resonance imaging in rectal cancer downstaged using neoadjuvant chemoradiation: accuracy of prediction of tumour stage and circumferential resection margin status. Colorectal Dis 2008 Mar 3.

(29) Nagtegaal ID, Marijnen CA, Kranenbarg EK, van d, V, van Krieken JH, Pathology Review Committee, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. American Journal of Surgical Pathology 2002;26(3):350-7.

(30) Baatrup G, Pfeiffer P, Svolgaard B, Jensen HA. Resectability of rectal cancers still fixed after radio-chemotherapy: evaluation by digital rectal examination, MRI, and intraoperative examination. International Journal of Colorectal Disease 2006;21(1):7-10.

(31) Kim JH, Beets GL, Kim MJ, Kessels AG, Beets-Tan RG. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? European Journal of Radiology 2004;52(1):78-83.

(32) Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. British Journal of Surgery 2006;90(3):355-64.

(33) Crane CH, Skibber JM, Birnbaum EH, Feig BW, Singh AK, Delclos ME, et al. The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer. International Journal of Radiation Oncology, Biology, Physics 2003;57(1):84-9.

(34) Coco C, Valentini V, Manno A, Mattana C, Verbo A, Cellini N, et al. Long-term results after neoadjuvant radiochemotherapy for locally advanced resectable extraperitoneal rectal cancer. Diseases of the Colon & Rectum 2006;49(3):311-8.

(35) Onaitis MW, Noone RB, Hartwig M, Hurwitz H, Morse M, Jowell P, et al. Neoadjuvant chemoradiation for rectal cancer: analysis of clinical outcomes from a 13-year institutional experience. Annals of Surgery 2001;233(6):778-85.

(36) Minsky BD, Cohen AM, Enker WE, Saltz L, Guillem JG, Paty PB, et al. Preoperative 5-FU, low-dose leucovorin, and radiation therapy for locally advanced and unresectable rectal cancer. Int J Radiat Oncol Biol Phys 1997 Jan 15;37(2):289-95.

(37) O'Neill BD, Brown G, Heald RJ, Cunningham D, Tait DM. Non-operative treatment after neoadjuvant chemoradiotherapy for rectal cancer. The Lancet Oncology 2007 Jul;8(7):625-33.

(38) Kim YH, Kim DY, Kim TH, Jung KH, Chang HJ, Jeong SY, et al. Usefulness of magnetic resonance volumetric evaluation in predicting response to preoperative concurrent chemoradiotherapy in patients with resectable rectal cancer. International Journal of Radiation Oncology, Biology, Physics 2005;62(3):761-8.

(39) Kim NK, Baik SH, Min BS, Pyo HR, Choi YJ, Kim H, et al. A comparative study of volumetric analysis, histopathologic downstaging, and tumor regression grade in evaluating tumor response in locally advanced rectal cancer following preoperative chemoradiation. International Journal of Radiation Oncology*Biology*Physics 2007 Jan 1;67(1):204-10.

```
ERROR: invalidrestore
OFFENDING COMMAND: --restore--

STACK:

-savelevel-
17764
(~d)
(~d)
17763
(~c)
(~c)
17762
(~b)
(~b)
17761
(~a)
(~a)
17760
(~‘)
(~‘)
17759
(~_)
(~_)
17758
(~^)
(~^)
17757
(~])
(~])
17756
(~\)
(~\)
17755
(~[)
(~[)
17754
(~Z)
(~Z)
17753
(~Y)
(~Y)
17752
(~X)
(~X)
17751
(~W)
(~W)
17750
(~V)
(~V)
17749
(~U)
(~U)
17748
(~T)
(~T)
17747
(~S)
(~S)
17746
(~R)
(~R)
17745
(~Q)
(~Q)
17744
(~P)
(~P)
17743
(~O)
(~O)
17742
```